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SPIEGEL, C EXAMINER

18N1/0513

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ART UNIT	PAPER NUMBER
1802	5

DATE MAILED: 05/13/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1/2/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), No days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-4, 8-10, 13-15 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 5-7, 11-12, 16-18 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-4, 8-10, 13-15 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

AMENDMENT ACKNOWLEDGED

The amendment filed January 2, 1996 (paper #4) is acknowledged and has been entered. Claims 1, 2, 4, 8, 9 and 13-15 have been amended. Claims 5-7, 11-12 and 16-18 have been cancelled. Claims 1-4, 8-10 and 13-15 are pending.

INFORMALITIES

The drawings are objected to for reasons of record (see PTO-948 attached to paper #3). Correction is required.

PRIOR CITATION OF TITLE 35 SECTIONS

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

NON-ART BASED REJECTIONS

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention.

The peaks on Figure 2 are not labelled. Applicant is cautioned against introducing new matter when making changes involving the drawings. Proposed drawing correction and/or the proposed substitute sheets of drawings must be embodied in a separate letter and show such changes in red ink (see page 142, Murthy, *Journal of Clinical Laboratory Analysis*, 8:140-143 (1994) where the peaks are labeled).

Claims 13-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 appears incomplete because the calculating step appears to require some means of either determining either erythrocyte adenylate kinase concentration/activity *per se* or differentially measuring what part of the total detection signal is attributable to erythrocyte adenylate kinase.

Claim 15, step d) is confusing because measurement of total fluorescence emission indicates total detection signal, not the total adenylate kinase activity/concentration, without correlation to a known standard. Similarly, calculation in step f) appears based upon relative fluorescence emissions rather than relative enzyme concentrations. Finally, --the-- should be inserted before "total" in line 13 for consistent language. In the alternative, the claims should refer to "total" activity versus "the/said total activity" when initially recited.

ART BASED REJECTIONS

The rejection of claims 1-18 under 35 U.S.C. § 103 as being unpatentable over Mainzer et al. (Chemical Abstract 78(13):82705, 1973) and Henry (CLINICAL DIAGNOSIS and MANAGEMENT by Laboratory Methods, 16th ed. 1979, pp. 985-1032) in view of Le Gall et al. (Biological Abstract 62035415, 1975), Buth et al. (Biological Abstract 71059076, 1981), Kurokawa et al. (Biological Abstract 91006139, 1991) and Koyama et al. (*Mol. Immunol.* 20(8):851-856, 1983) is withdrawn in view of applicant's amendments and arguments.

Claims 1, 13 and 14 are rejected under 35 U.S.C. § 103 as being unpatentable over Olsson et al. (*Journal of Applied Biochemistry*, 5: 437-445 (1983)).

Claims 2, 3 and 15 are rejected under 35 U.S.C. § 103 as being unpatentable over Olsson et al. (*Journal of Applied Biochemistry*, 5: 437-445 (1983)) as applied to claims 1and 13 above, and further in view of Tsuji et al. (Chemical Abstract 86:39099) or Friedrich et al. (*Biochemical Genetics* 22(5/6):389-394 (1984)) and, if necessary, further in view of Buth et al. (Biological Abstract 71059076, 1981).

Claims 4 and 8-10 are rejected under 35 U.S.C. § 103 as being unpatentable over Olsson et al. (*Journal of Applied Biochemistry*, 5: 437-445 (1983)) as applied to claims 1and 13 above, and further in view of Matsuura et al. (*Journal of Biological Chemistry*, 264 (17): 10148-101555 (1989)).

The claimed invention is directed to (I) detection of hemolysis and/or conditions producing hemolysis by measuring serum adenylate kinase; and, (2) determination of serum erythrocyte adenylate kinase activity.

Olsson et al. found that (i) adenylate kinase whas concommitantly released with hemoglobin during cell aging; (ii) cell aging results in progressive lysis of erythrocytes; (iii) adenylate kinase was suitable for monitoring cell lysis due its extreme storage stability; (iv) there was a high degree of correlation between the amount of accumulated hemoglobin and adenylate kinase; and, (v) while hemolysis was conventionally measured by measurement of extracellular hemoglobin, adenylate kinase activity measurement was also a sensitive and

convenient way to follow hemolysis. An advantage of measuring adenylate kinase lies in studying the lysis of other cell types, e.g. platelets. (see page 437; Table I; page 445). Olsson et al. determined adenylate kinase activity in plasma by measuring formation of ATP from ADP by the firefly luciferase reaction. DAPP, which is a specific inhibitor of erythrocyte adenylate kinase, confirmed the origin of the adenylate kinase in the plasma to be erythrocytic (page 442). Thus, Olsson et al. differs in detecting hemolysis by determining erythrocyte adenylate kinase activity in plasma rather than in serum. However, it would have been obvious to one of ordinary skill in the art to modify the method of Olsson et al. by determining erythrocyte adenylate kinase activity in serum rather than plasma because serum and plasma are conventional alternative samples used in clinical analysis derived from whole blood.

Olsson et al. also differs in failing to disclose alternative methods for determining erythrocyte adenylate kinase activity, e.g. including use of gel electrophoresis and immunochemistry, which differentiate adenylate kinase activity of erythrocytic origin from adenylate kinase from other cells. Tsuji et al. measure erythrocyte adenylate kinase by agarose thin-layer gel electrophoresis with tetrazolium (i.e. formazan) visualization. Friedrich et al. describe electrophoretic separation and visualization of human erythrocyte adenylate kinase. Buth et al. use NAD-dependent glucose-6-phosphate dehydrogenase in adenylate kinase enzyme staining/detecting procedures because it significantly less expensive than utilizing NADP. Matsuura et al. describe immunoblot analysis of human erythrocyte adenylate kinase (AK1). Thus, it would have been further obvious and well within ordinary

skill in the art to measure erythrocyte adenylate kinase by any known and conventional assay, including electrophoretic separation and staining, such as with an NAD-dependent glucose-6-phosphate dehydrogenase visualization technique; immunoassay, etc. as suggested by Tsuji et al., Friedrich et al., Buth et al., and/or Matsuura et al.

REMARKS

In conclusion, applicant's amendments and arguments filed January 2, 1996 have been fully considered but are not deemed convincing of patentability for the reasons *supra*, for other reasons already of record, and in view of the new grounds of rejection *supra*.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Sock et al. (*Analytical Biochemistry* 171:310-319 (1988)) describe a blotting method for detecting adenylate kinase on electrophoretograms.

Borglund et al. (*Upsala Journal of Medical Sciences*, 83(2):81-84 (1978)) describe fluorometric microassays for adenylate kinase.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 308-4065.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel
May 2, 1996

Carol A. Spiegel

CAROL A. SPIEGEL
PRIMARY EXAMINER
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